## REMARKS

**Amendments**

The related applications section is updated to refer to the issued grandparent application.

Claims 13-19 are added herein with support for those claims being found at least as follows: claim 13 (claim 1); claim 14 (claim 6); claim 15 (claim 5); claim 16 (page 2, lines 26-27); claim 17 (claim 3); claim 18 (claim 4); and claim 19 (claims 1, 4 and 6).

In that the amendments do not introduce new matter, entry thereof is respectfully requested.

**Restriction**

The Examiner notes the election of the medulloblastoma species, but states that the search has been extended to the next species "carcinoma."

**Priority**

The Examiner contends that claims drawn to a method of treating medulloblastoma are given the priority date of the current filing date 6/27/2003. While noting that this conclusion does not form the basis for any stated objection or rejection, and therefore preserving the right to traverse this finding in the event it does form the basis of an actual objection or rejection, Applicants do not dispute that the word "medulloblastoma" is not expressly recited in 60/141,316 or 10/268,501.

**Specification**

The Examiner objects to the specification on the basis that there is allegedly no brief description for Figure 8B and 8C under the "Brief Description of the Drawings" on page 7, line 10.

Applicants respectfully disagree. Page 7, lines 9-10 explains that Figures 8A, B, and C show binding of Fab 2C4 and several humanized 2C4 variants to ErbB2 ECD - each of the figures shows the data for a different group of variants identified in the key in each figure. Hence, Applicants submit that Figures 8B and 8C are described on page 7. Reconsideration of the objection is respectfully requested.

**Section 112, 2nd paragraph**

The Examiner rejects claims 3-5 as vague and indefinite for reciting the terms 2C4 and 4D5 as the sole means of identifying the claimed molecules.

Applicants respectfully traverse the rejection. Applicants submit that the terms are clear when read in light of the specification. See, in particular, page 14, line 33 through to page 15, line 4 for a definition for "monoclonal antibody 2C4" and page 15, lines 5-11 for a definition for "monoclonal antibody 4D5." Notwithstanding this, without acquiescing in the rejection, and in order to expedite prosecution, Applicants have amended claim 3 to refer to the deposit of the 2C4 monoclonal antibody, and claim 5 to refer to the deposit of the 4D5 antibody. Claim 4 now depends on amended claim 3.

Reconsideration and withdrawal of the rejection is respectfully requested.

**Section 112, 1st paragraph - claims 3-5**

Claims 3-5 are rejected under 35 USC Section 112, first paragraph as failing to comply with the enablement requirement.

Applicants submit that the deposited antibodies are not necessary to practice the claimed invention, since, for example, the sequences thereof are known or disclosed in the application, and this information could be used by the skilled person to make or identify an antibody as in claims 3-5. Notwithstanding this, Applicants provide the following statement as to the deposited 2C4 and 4D5 antibodies.

Monoclonal antibodies 2C4 and 4D5 were deposited with the American Type Culture Collection, 1801 University Boulevard, Manassas, VA20110-2209 (ATCC) as follows:

| **Antibody** | **ATCC No.** | **Deposit Date** |
|---|---|---|
| 4D5 | ATCC CRL 10463 | May 24, 2990 |
| 2C4 | ATCC-HB-12697 | April 8, 1999 |

The undersigned states that these deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposits for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an

agreement between Genentech, Inc. and ATCC, which assures that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent, assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC § 122 and the Commissioner's rules pursuant thereto (including 37 CFR § 1.14 with particular reference to 886 OG 638).

Reconsideration and withdrawal of the Section 112, 1st paragraph rejection of claims 3-5 is respectfully requested.

**Section 112, 1st paragraph - claims 1-6**

Claims 1-6 are rejection under 35 USC Section 112, first paragraph as failing to comply with the enablement requirement. These claims are rejected on the basis that the claimed invention is allegedly not enabled for therapy of medulloblastoma.

The Examiner relies on Bickel *et al. Advanced Drug Delivery Reviews* 46: 247-279 (2001) as teaching that peptide and protein therapeutics are generally excluded from transport from blood to brain, owing to the negligible permeability of these drugs to the brain capillary endothelial wall which makes up the blood-brain barrier (BBB) *in vivo*. In addition, the Examiner relies on Jain, *Sci. Am.* 171(1): 58-65 (1994), as disclosing barriers to the delivery of drugs into solid tumors. An MSNBC News Services report on a drug unrelated to those claimed (Endostatin) is relied on as illustrating that treatment of cancer in a host is "quite unpredictable." Finally, an article by Gura *et al. Science* 278: 1041-1042 (1997), is relied upon for demonstrating that treatment of cancer in general is at most unpredictable.

Applicants submit that the presently claimed invention is enabled.

First, Applicants direct the Examiner's attention to Grossi *et al., Clinical Cancer Research* 9:5514-5520 (2003), copy attached, which discloses that HER2 antibodies, such as those claimed, have some - albeit diminished - efficacy following intravenous administration in treating brain tumors. See

introduction on page 5514. Such efficacy can be enhanced by direct administration to the brain. Indeed, Grossi *et al.* conclude that intracerebral microinfusion of trastuzumab (HERCEPTIN®) is safe and superior to systemic delivery as therapy for HER2-expressing intracerebral neoplasms. Administration schemes for directed administration to the brain are taught by the present application; see, for example, page 48, lines 8-11, of the specification, which refers to intracerebrospinal and intrathecal administration. Thus, Applicants submit that Grossi *et al.* refutes any conclusions that might be made in view of Bickel *et al.* concerning delivery of HER2 antibody therapeutics to the brain.

Second, as to whether HER2 antibodies generally have efficacy in treating solid tumors, Applicants point out that one of the exemplified antibodies, HERCEPTIN®, was approved by the FDA in 1998 for therapy of solid (breast) tumors (page 2, lines 26-30). As to the other exemplified antibody, rhuMAb 2C4 (Pertuzumab; OMNITARG®), this drug has also shown clinical activity in treatment of solid tumors in humans. See, for example, Agus *et al.*, *Proceedings of the American Association for Cancer Research* (Abstract No. 771) 22:192 (2003); Agus *et al.*, "Clinical Activity in a Phase I Trial of HER2-Targeted rhuMAb 2C4 (pertuzumab) in Patients with Advanced Solid Malignancies" (Slides presented at the 2003 ASCO Annual Meeting) pps. 1-32 (2003); Gordon *et al.*, *Journal of Clinical Oncology* (Abstract #5051 from the 41st Annual Meeting of ASCO)23(16S):467s (Jun 1, 2005); and Gordon *et al.*, "Clinical activity of pertuzumab (rhuMab 2C4) in advanced, refractory or recurrent ovarian cancer and the role of HER2 activation status" (Poster #5051 from the 41st Annual Meeting of the American Society of Clinical Oncology (ASCO))(May 15, 2005), copies attached. Thus, Applicants submit that this evidence illustrates that HER2 antibodies have efficacy in solid tumor therapy. Such evidence addresses the Examiner's reliance on Jain, Gura *et al.* and the MSNBC News Report for supposedly showing that cancer therapy in general is unpredictable.

In summary then, Applicants submit that the evidence provided herewith addresses and obviates the Examiner's bases for rejecting the claims for lack of enablement under 35 USC Section 112, first paragraph. Reconsideration and withdrawal of the enablement rejection is respectfully requested.

**Section 102(b)**

Claims 1, 2, 3 and 5 are rejected under 35 USC 102(b) as being anticipated by WO 98/17797 as evidenced by Shepard *et al. J. Clin. Immunol.* 11(3): 117-126

(1991).

Claims 1, 2 and 5 are rejected under 35 USC Section 102(b) as being anticipated by Hudziak *et al.* (US Patent No. 5,725,856).

These rejections are obviated by the amendment of claim 1 to delete "carcinoma" from the Markush group therein. Reconsideration and withdrawal of the rejections in view of the amendment is respectfully requested.

**Section 103**

Claims 1-5 are rejected under 35 USC Section 103(a) as being unpatentable over WO98/17797 in view of Schaefer *et al.* *Oncogene* 15: 1385-1394 (1997), and as evidenced by Shepard *et al.*

Claims 1-5 are rejected under 35 USC Section 103(a) as being unpatentable over Hudziak *et al.* in view of Shepard *et al.* and Schaefer *et al.*

These rejections are obviated by the amendment of claim 1 to delete "carcinoma" from the Markush group therein. Reconsideration and withdrawal of the rejections in view of the amendment is respectfully requested.

**Double patenting**

Claims 1-5 are provisionally rejected under 35 USC 101 as claiming the same invention of that as claims 1-5 of copending application No. 10/268,501.

This rejection is obviated by the amendment of claim 1 to delete "carcinoma" from the Markush group therein. Reconsideration and withdrawal of the rejections in view of the amendment is respectfully requested.

**Obviousness-type double patenting**

Claims 1 and 5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 11 and 15-18 of US Patent No. 5,725,856 and over claims 1, 6, 11 and 13 of US Patent No. 5,770,195.

Claims 1 and 5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 11 and 15-18 of US Patent No. 6,627,196B1.

These rejections are obviated by the amendment of claim 1 to delete "carcinoma" from the Markush group therein. Reconsideration and withdrawal of the rejection in view of the amendment is respectfully requested.

**Section 102(f)**

Claims 1-5 are rejected under 35 USC Section 102(f).

This rejection is obviated by the amendment of claim 1 to delete "carcinoma" from the Markush group therein. Reconsideration and withdrawal of the rejection in view of the amendment is respectfully requested.

**Related Case Statement**

Applicants ask the Examiner to consider the following US applications that are related to the above application:

U.S. Serial No. 11/429,043, filed 5/5/2006

U.S. Serial No. 11/429,361, filed 5/5/2006

U.S. Serial No. 11/429,363, filed 5/5/2006

Other related US patents and applications have been cited in Information Disclosure Statements (IDSs) as issued US patents or published US-A publications, and Applicants requests that the Examiner likewise consider those related patents and applications.

Applicants note that an IDS was filed on 4/19/2006 citing refs. 350-353, and respectfully request consideration of same, and return of the initialed PTO-1449 form indicating those references have been considered.

Respectfully submitted,
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